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(54) Title: STABILIZED CYCLODEXTRIN COMPLEXES

(57) Abstract: Smooth, stable, spherical and uniform cyclodextrin complex particles are formed by employing an emulsifying agent and vigorous stirring and/or homogenizing to form a uniform aqueous dispersion of cyclodextrin-guest complex, and then recovering the resulting complex particulate.

STABILIZED CYCLODEXTRIN COMPLEXES

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a method for forming a cyclodextrin complex and, more specifically, a method for forming complexes of a cyclodextrin and a guest molecule which are smooth, stable, uniform and spherical.

2. Description of Related Art

Cyclodextrins, also called "Schardingers dextrins", cycloamyloses, cyclomaltoses and cycloglucans, are oligomers of anhydroglucose, bonded together by alpha 1,4 bonds to form a ringed compound. A six membered ring is called alpha cyclodextrin; seven, beta cyclodextrin; and eight, gamma cyclodextrin. These six, seven and eight membered rings are also referred to as cyclomaltohexaose, cyclomaltoheptaose and cyclomaltoctaose, respectively.

Conventionally, cyclodextrins are obtained by treating a

starch slurry with enzyme or acid to produce a gelatinized and liquefied slurry having a DE between 1 and 5. The gelatinized and liquefied starch slurry is then treated with cyclodextrin glycosyltransferase (CGT), at the appropriate pH, temperature and time for the selected CGT. The enzyme, CGT, is obtained from microorganisms such as Bacillus macerans, B. magaterium, B. circulans, B. stearothermohiilus, and Bacillus sp. (alkalophilic) as well as others. The resulting digest from treatment of a gelatinized and liquefied starch slurry with CGT is then subjected to a separation and purification process to obtain cyclodextrins.

One of the commercially important aspects of cyclodextrins is their ability to form complexes with other chemical compounds. Physically, a cyclodextrin is toriodal in shape. The interior of the cavity is hydrophobic while the exterior is somewhat hydrophilic. The consequence of this is that cyclodextrins are able to form inclusion complexes with substances that are less polar than water and have at least one outer geometric dimension corresponding to the diameter of the cyclodextrin cavity. Often the exterior of the cyclodextrin is modified to increase its hydrophilic nature. The cyclodextrin or modified cyclodextrin can be complexed with an insoluble or hydrophobic compound thereby forming a hydrophilic complex. In simple terms, this allows a compound which is insoluble in water to become soluble in water.

Cyclodextrin complexes are being employed in foods, pharmaceuticals, cosmetics, agricultural and chemical fields to act as a means for delivering a guest molecule. The cyclodextrin is used not only to solubilize a guest but also to stabilize the guest or allow for slow release of the guest. Typically, the guest is a flavor, a fragrance, a drug, an insecticide, or another key ingredient or component.

The most widely used method for forming a complex between a cyclodextrin and a guest molecule involves dissolving the cyclodextrin and guest molecule in water and collecting the precipitate that forms. This precipitate is technically an agglomerate of a plurality of complexes. One of the problems with such a process is that the recovered precipitate is rod-like in shape and increases in size over time such that different sized agglomerates are formed. The different sized agglomerates yield uneven distribution of the complexes in the resulting composition. This uneven distribution can result in problems when the complex is used in a pharmaceutical application such as a drug.

Besides uneven distribution, these agglomerates also provide a grainy appearance and a gritty feel to the composition in which the complex is employed. The gritty feel and grainy appearance of the complex are undesirable in both foods and cosmetics. There is

a need for a method to produce cyclodextrin complexes wherein the resulting agglomerates of complexes are smooth, stable, and uniform in distribution.

Dry or semi-dry methods have also been suggested for forming a complex of cyclodextrin and guest. For example, U.S: Patent Nos. 5,635,238; 5,580,851; 5,571,782; 5,552,378; and 5,543,157 teach a method for kneading cyclodextrin and a guest molecule to form complexes. Also, U.S. Patent No. 5,007,966 teaches a method for using a ball mill to form complexes between cyclodextrin and a guest molecule. Although these methods can produce a small particulate complex agglomerate, they do not necessarily provide a smooth, spherical uniform complex.

Another problem in the field of cyclodextrins is the relatively low water solubility of beta cyclodextrin. Beta cyclodextrin is currently the only cyclodextrin which is Generally Recognized As Safe (GRAS) for foods. It is also considered to be one of the most versatile of the cyclodextrins in its ability to complex with a variety of guest molecules. To date, the solution to the low solubility problem of beta cyclodextrin has been to chemically modify the cyclodextrin. The problem with chemical modification is that chemically modified beta cyclodextrin is not currently GRAS for food. Additionally, such modification can alter

the complexation properties of the cyclodextrin and produce impurities which are difficult to separate from the product. There is a need to increase the water solubility of beta cyclodextrin without the need to chemically modify it.

SUMMARY OF THE INVENTION

Applicants have now discovered that, by using an emulsifying agent during the process of making the cyclodextrin complex, the resulting complex agglomerates take the form of small spherical particles which are smooth, stable and uniform in distribution. The complexation process is conducted in water and the resulting cyclodextrin-guest complex agglomerates are encapsulated by the emulsifying agent. The term emulsifying agent will be used throughout the specification and claims to refer to both an emulsifier and an emulsion stabilizer.

Broadly, the process of the present invention entails combining water, cyclodextrin, a guest molecule and an emulsifying agent; and then mixing these components to form a uniform dispersion in water. The particulate portion of the dispersion comprises the cyclodextrin complexed with the guest molecule with the emulsifying agent acting to stabilize the complexes. Optionally, a starch hydrolysate such as a corn syrup or a maltodextrin can be combined with the other components prior to

mixing. The starch hydrolysate forms part of the particulate of the dispersion. The mixing must be vigorous enough to provide a uniform dispersion. Any order of adding and mixing can be employed, however, it is preferred to form the complex first by combining the water, guest molecule and cyclodextrin; mixing these components; and then adding the emulsifying agent and optional starch hydrolysate while continuing to mix. The agglomerated complexes can be recovered by drying the mixture to provide a particulate material.

The starch hydrolysate is preferably employed when the resulting agglomerate is intended for use as a dried product or is intended to be dried and stored for a period of time. The starch hydrolysate provides the dried particulate with protection against oxygen and deterioration of the guest molecule due to oxidation. Such protection is generally not necessary when the product is used in an aqueous medium.

DETAILED DESCRIPTION OF THE INVENTION

All the components can be combined and then mixed or they can be combined and mixed a few at a time with the separate mixtures being combined and mixed to form the final dispersion. In one preferred embodiment, water, cyclodextrin and a guest are combined and mixed in one step and the emulsifying agent with or without the

starch hydrolysate is mixed with water in a separate step, then the two mixtures are combined and mixed to form the uniform dispersion.

The mixing of the components must be such that a uniform dispersion is formed. Preferably, a homogenizer is used to form the mixture. Suitable homogenizers include colloidal mills and high speed mixers/blenders. The homogenizer is used in a conventional manner to form the dispersion. A kneader device can be used provided a sufficient amount of water is present to allow the emulsifying agent to have an effect on the particle size and stability during the drying step.

In one preferred embodiment, the cyclodextrin and guest are combined and mixed in water for an extended period of time, for example, about two or more hours, to cause complexation to occur while the emulsifying agent, with or without the starch hydrolysate, is mixed in water also for an extended period of time, for example, about two or more hours, and then these two mixtures are mixed in a homogenizer to form the dispersion.

In another preferred embodiment, the cyclodextrin and guest are combined and mixed in water for a short period of time, for example, about ten minutes, to cause complexation to occur while the emulsifying agent, with or without the starch hydrolysate, is

mixed in water also for a short period of time, for example, about ten minutes, and then these two mixtures are combined and mixed in a homogenizer to form the dispersion. Complexation can, in some instances, take place fairly rapidly, however, it has been found that complexation is dependent upon the guest molecule and its interaction with cyclodextrin.

Preferably, the combining and mixing steps are conducted at ambient temperature.

The mixing time is sufficient to cause complexation. As recognized, complexation can occur fairly rapidly. Mixing can be divided into two steps. One step to cause complexation and a second step to cause formation of a uniform dispersion/emulsion. Alternatively, mixing is conducted all at once to cause both complexation and formation of the uniform dispersion/emulsion. As brought out above, it is preferred that the mixing be in two steps, a first step to cause complexation and a second step with a homogenizer to form the uniform dispersion/emulsion. The first mixing step, to cause complexation, is done in a less vigorous manner than the second step.

Preferably, the complexes are recovered from their aqueous environment, in a conventional manner using conventional equipment.

One preferred method is to spray dry the dispersion/emulsion. Such a step produces a powdery, dry particulate which comprises a complex of cyclodextrin and guest encapsulated by emulsifying agent. Where a starch hydrolysate has been employed, the particulate recovered from the spray drying operation also has the dried starch hydrolysate present in the dried particulate.

The cyclodextrin employed in the present invention includes alpha cyclodextrin, beta cyclodextrin, gamma cyclodextrin, modified alpha cyclodextrin, modified beta cyclodextrin, modified gamma cyclodextrin, a branched alpha, beta or gamma cyclodextrin, or combinations thereof. The process of the present invention has been found to work especially well with beta cyclodextrin because it increases the efficiency in forming complexes with beta cyclodextrin. Suitably, the cyclodextrin which is combined with the other components is in liquid form, e.g. an aqueous slurry of cyclodextrin.

Suitable guest molecules employed in the present invention include food additives, drugs, cosmetic components, insecticides, flavors, fragrances, pharmaceutical ingredients, agrochemical ingredients, biocides and pesticides.

Suitable starch hydrolysates for use in the present invention

include corn syrups, corn syrup solids and maltodextrins. Good results have been obtained with maltodextrins having a Dextrose Equivalent (DE) of about 5. Good results have been obtained with corn syrups having a DE of 36. Suitably, the starch hydrolysate which is combined with the other components is in liquid form, e.g. an aqueous slurry of starch hydrolysate, such as a corn syrup.

Suitable emulsifying agents for use in the present invention include carbohydrate-based emulsifiers and especially starch-based emulsifiers. Preferably, the starch-based emulsifiers are starch alkenyl succinates. Good results have been obtained with starch octenyl succinate and especially a hydrolyzed n-octenyl succinate of starch. Suitable emulsifiers for use in the present invention include propylene glycol monostearate, polyglycerol monostearate, ethoxylated monoglyceride and lecithin. Suitable emulsion stabilizers for use in the present invention include hydrolyzed n-octenyl succinate of starch (n-OSAN starch), Gum Arabic, Gum Tragacanth and Gum Ghatti.

The cyclodextrin:guest molar ratio in the water is preferably between about 0.5:1 to about 5:1 and, more preferably, between about 0.75:1 to about 2:1. Good results have been obtained with a molar ratio of about 1:1, i.e. one mole of cyclodextrin to one mole of guest.

The amount of emulsifying agent used in the present invention is preferably about 1% to about 30% based on the total weight of the components in the combination and, more preferably, about 5% by weight to about 20% by weight. Good results have been obtained with about 10% by weight.

The amount of water used in the present invention is conventional. Preferably, the mixture comprises at least 50% by weight water based on the total weight of components in the combination.

The amount of starch hydrolysate used in the present invention is preferably about 0% to about 30% based on the total weight of the components in the combination and, more preferably, about 5% by weight to about 15% by weight. Good results have been obtained with about 10% by weight.

These and other aspects of the present invention may be more readily understood by reference to one or more of the following examples.

EXAMPLE I

This example illustrates that n-OSA starch helps reduce the complex particle (agglomerate) size through homogenization and that

the formation of a CD/active complex step is preferable prior to adding an emulsifying agent. The results of this example are illustrated in Table 1 below.

TABLE 1

Trial	Formula (% by Weight)	Median Particle Size (micron)
A	28%BCD+7%Oil+65%DIW	14.6
B	14%BCD+14%MDX+7%Oil+65%DIW	44.6
C	14%BCD+7%n-OSA+7%CSS+7%Oil+65%DIW	9.6
D	14%BCD+7%n-OSA+7%CSS+7%Oil+65%DIW	5.6
E	14%BCD+14%n-OSA+72%DIW	37.9

Abbreviations used in the examples:

BCD = beta cyclodextrin

MDX = maltodextrin (5 DE) (a starch hydrolysate)

DIW = Deionized water

Oil = Orange oil (guest)

n-OSA = C*EmCap Instant from Cerestar USA, an n-octenyl succinate of starch (emulsifier)

CSS = Corn syrup solid (36 DE) (a starch hydrolysate)

For Trials A, B, C and E, all the ingredients in the formulas were mixed in a plastic jug and placed in a sample shaker at 200 rpm for 12 hours at room temperature. For Trial D, one half of the water was mixed with the BCD while the other half of the water was mixed with the oil, n-OSA and CSS. These two mixtures, in separate

jugs, were shaken at 200 rpm for 12 hours at room temperature, and then they were combined.

After shaking, each formula, including the combined formula D, was blended in a Waring blender at high speed for 2 minutes with 65% power, followed by homogenization in a Gaulin Homogenizer (Gaulin, Everett, MA) with a first step pressure of about 3000-3500 psig and a second step pressure of about 500-800 psig. The homogenized samples were tested on a Brinkmann Particle Size Analyzer for size distribution.

As the median particle size values in the Table show, Trials C and D gave the finest particles, indicating effect of n-OSA (emulsifier) on BCD complex particle sizes. When BCD complexes are performed without the presence of n-OSA, the particle sizes were finer after homogenization (Trial D versus Trial C). Microscopic examination of the final products showed that Trial D gave spherical particles while other trials gave mostly irregularly-shaped crystals among rod-shaped and plate-shaped crystals.

Trial E did not result in an emulsion-like product and BCD crystals precipitated immediately after homogenization. This shows that n-OSA interacts with BCD-oil complexes, not with BCD, to reduce the particle sizes.

EXAMPLE II

This example illustrates that multiple passes in the homogenizer effectively reduce particle sizes of BCD complexes without pre-formation of the complexes in absence of an emulsifier.

TABLE 2

Trial	Formula (% by Weight)	Median Particle Size (micron)	
		1st Pass	2nd pass
F	14%BCD+14%n-OSA+7%Oil+65%DIW	53.4	3.7
G	14%BCD+14%n-OSA+7%Oil+65%DIW	19.3	6.4

For Trial F, all the ingredients except oil were mixed to allow dissolution of the emulsifier before oil was added. The whole formula was blended in a Waring blender at high speed for 2 minutes before going through the Gaulin Homogenizer as described in Example I. A sample was taken for particle size analysis and the rest of the product was fed through the homogenizer for one second pass under the same processing conditions. As the particle size data show, the second pass significantly reduced the particle sizes.

Trial G was done a little differently from Trial F although the total formula was the same. In Trial G, half of the water was used to dissolve the emulsifier and the other half of the water was mixed with BCD and oil.

Only the mixture of BCD/oil in water was blended in a Waring blender and processed for the first pass of homogenization. After the first pass and sample taking, the emulsifier solution was added and blended in a Waring blender before the second pass of homogenization.

EXAMPLE III

This example illustrates that BCD complexes in the present invention have better storage stability.

TABLE 3

Trial	Formula (% by Weight)	Median Particle Size (micron)	
		Fresh	20 Days
H	28%BCD+5%Oil+67%DIW	10.5	56.4
I	14%BCD+7%n-OSA+7%CSS+7%Oil+65%DIW	5.5	6.2

Trial H used the same procedure as for Trial A except for the formula and Trial I was replicate of Trial D. After 20 days of storage of the emulsions at room temperature, without emulsifier, the particle sizes increased greatly, while with the emulsifier, the particle sizes showed good stability.

EXAMPLE IV

This example illustrates forming complexes with a fish oil in accordance with the present invention and then drying the complex by a freeze drying technique. The formulation using a blend of

BCD, n-OSA and CSS (Trail M) delivered the highesr amounts of total oil and omega-3 fatty acids. Moreover, Trial M gave a powdered fish oil without detectable fishy odor.

TABLE 4

Trial	Carrier (carrier ratio w/w)	Total Oil	ω-3 Fatty Acids, g/100 g Powder
J	GCD	31.1%	7.8
K	BCD	37.7%	10.2
L	n-OSA/CSS (1:1)	30.1%	8.4
M	BCD/n-OSA/CSS (4:1:1)	42.6%	11.7

GCD = gamma cyclodextrin

Oil = OmegaPure™ Fish Oil (Omega Protein, Inc.)

For Trials J, K, and M, all the ingredients, including carrier materials listed above, water, and fish oil (40% w/w of solids) were mixed in a plastic jug and placed in a sample shaker at 250 rpm for 23 hours at 37°C. For Trial M, two thirds of the water was mixed with BCD and the oil while the one third of the water was mixed with n-OSA and CSS. These two mixtures, in separate jugs, were shaken at 250 rpm for 23 hours at 37°C, and then were combined. The combined mixture was homogenized using a hand-held homogenizer, as those of Trials J, K, and M. Each emulsion was then freeze dried to yield a powder product.

A sensory test on the products showed that Trial L product has an obvious rancid odor, and that Trial K product has a very faint fish odor while products from Trials J and M did not have detectable fish odor.

EXAMPLE V

This example illustrates preparation of powdered complexes of fish oil with a blend of BCD, n-OSA and CSS using a spray drying technique.

To the mixed carriers (25% BCD, 12.5% n-OSA, and 12.5% CSS, all on dry basis, w/w), water was added in an amount that would give approximately 60% solids in the final formula. Fish oil (50% w/w of solidswas then added to the slurry, mixed, homogenized in a conventional manner. The emulsion was subsequently spray dried at inlet temperature of 330°C and outlet temperature of 150°C. The resultant powder contains about 41% of fish oil, giving total omega-3 fatty acids of 11.4 grams per 100 grams of powder. Analysis of fatty acid composition (AOAC Official Method Ce 1b-89) shows no significant difference between fresh fish oil and the fish oil extracted from the powder.

It will be understood that the claims are intended to cover

all changes and modifications of the preferred embodiments of the invention herein chosen for the purpose of illustration which do not constitute a departure from the spirit and scope of the invention.

What is claimed is:

1. A method for forming a cyclodextrin-guest complex comprising:

(a) forming a combination comprising water, a cyclodextrin, a guest molecule and an emulsifying agent;

(b) mixing said combination to form a uniform dispersion in water of said emulsifying agent and a complex of said cyclodextrin and said guest molecule.

2. The method of claim 1 further comprising:

(c) recovering said emulsifying agent and said complex as a particulate.

3. The method of claim 1 wherein said combination further comprises a starch hydrolysate, and said uniform dispersion includes said starch hydrolysate.

4. The method of claim 3 wherein said mixing is performed by an homogenizer.

5. The method of claim 4 wherein said homogenizer is a colloidal mill, a high speed mixer/blender, or a combination thereof.

6. The method of claim 2 wherein said recovery is accomplished by spray drying said uniform dispersion.

7. The method of claim 1 wherein said cyclodextrin is alpha cyclodextrin, beta cyclodextrin, gamma cyclodextrin, a modified alpha cyclodextrin, modified beta cyclodextrin, modified gamma cyclodextrin, or a combination thereof.

8. The method of claim 1 wherein the guest molecule is a food additive, a drug, a cosmetic, an insecticide, a flavor, a fragrance, a pharmaceutical ingredient, an agrochemical ingredient, or a pesticide.

9. The method of claim 1 wherein said forming of said combination comprises:

(a1) combining and mixing water, cyclodextrin and guest molecule to form a complex of cyclodextrin and guest, and form a complex-water mix;

(a2) combining and mixing water and emulsifying agent to form an emulsifier-water mix; and

(a3) combining and mixing said complex-water mix and said emulsifier-water mix to form said combination.

10. The method of claim 1 wherein said forming of said

combination comprises:

(a1) combining and mixing water, cyclodextrin, guest molecule and emulsifying agent to form complexes between said cyclodextrin and said guest molecule.

11. The method of claim 9 wherein said mixing in steps (a1) and (a2) lasts about 12 hours.

12. The method of claim 10 wherein said mixing in step (a) lasts about 12 hours.

13. The method of claim 1 wherein said emulsifier is a carbohydrate-based emulsifying agent.

14. The method of claim 13 wherein said emulsifying agent is a starch alkenyl succinate.

15. The method of claim 14 wherein said emulsifying agent is n-octenyl succinate of starch.

16. The method of claim 3 wherein said starch hydrolysate is a maltodextrin, corn syrup and/or corn syrup solids.

17. A cyclodextrin-guest complex made by the process of

claim 2 wherein the complex is a dry particulate encapsulated by said emulsifying agent.

18. A cyclodextrin-guest complex made by the process of claim 3 wherein said complex is recovered as a particulate comprising a starch hydrolysate product and a complex of cyclodextrin and guest molecule encapsulated by said emulsifying agentier.

INTERNATIONAL SEARCH REPORT

Int tional Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08B37/16 A61K47/48 A23L1/0522

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08B A61K A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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